



Benralizumab: an anti-IL-5 receptor α monoclonal antibody in the treatment of asthma

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IL-5 is a key cytokine responsible for the maturation, recruitment and survival of eosinophils. The role of eosinophils in pathomechanisms of severe asthma and association of those cells with frequent exacerbations are well accepted. Novel biologic agents including anti-IL-5 antibodies (mepolizumab and reslizumab) as well as anti-IL-5 receptor α chain (benralizumab) have been developed. Benralizumab (FasenraTM) leads to reduced eosinophil counts in airway mucosa, blood, sputum and a clear inhibition of eosinophil differentiation and maturation in the bone marrow. In clinical studies, benralizumab significantly reduces the rate of asthma exacerbations and has a clear oral glucocorticoid sparing effect. The frequency and the type of reported adverse events do not differ between active treatment and placebo arms.

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Eosinophils play a key role in inflammation underlying pathomechanisms of asthma, allergic disorders and other lung diseases. IL-5 together with IL-3 and GM-CSF are vital for production, maturation, recruitment and survival of eosinophils at the site of inflammation. The role of eosinophils in allergic, Th2 or T2 type inflammation, association of those cells with frequent exacerbations [1], and in general good responsiveness of eosinophilic inflammation to treatment with corticosteroids is nowadays well accepted [2]. However, the role of eosinophils and chronic inflammation in asthma, which is fundamentally a disease characterized by bronchial smooth muscle hyperresponsiveness, requires further studies. What is interesting, recently it has been suggested that besides the classical Th2 pathway, typical for allergic, eosinophilic asthma, other immunologic mechanisms, such as the epithelial-innate lymphoid cell type 2 (ILC2) pathways, may be involved in the development of nonallergic eosinophilic inflammation in asthma and chronic obstructive pulmonary disease (COPD) [3]. It might also be hypothesized that allergy may be an epiphenomenon given that bronchial epithelial cell triggered by several potential stimuli produce alarmins such as IL-33 and thymic stromal lymphopoietin (TSLP) that drive Th2-type inflammation partly via ILC2 cells, and IgE production requires local production of IL-4 and IL-13 to induce B cell IgE switching. Thus, anti-IL5 therapy is not reserved only for atopic subjects. Patients with severe asthma phenotype have typically other comorbidities including nasal polyps and rhinosinusitis. ILC2s are involved in the pathomechanisms of chronic rhinosinusitis and are able to produce substantial amounts of IL-5 and IL-13. Thus, Brusselle and Bracke [3] raised a hypothesis that patients with adult-onset, nonallergic severe eosinophilic asthma may represent interesting target for anti-IL-5 or anti-IL-13 treatment. Several studies based on animal models proved that interference with IL-5 pathway may impact allergen-induced airway eosinophilia, and hyperresponsiveness [4], thus representing an interesting target for therapeutic intervention. Several monoclonal antibodies (mAbs) including anti-IL-5 antibodies (mepolizumab and reslizumab) as well as anti-IL-5 receptor (anti-IL-5R) α chain (benralizumab) have been developed, and their efficacy and safety in patients with asthma have been evaluated in clinical trials [5,6]. In the latest review, Bel and Ten Brinke [7] pointed out that novel anti-IL-5 biologic agents have demonstrated promising results for many patients with asthma and COPD who have eosinophilic airway inflammation. However,

the heterogeneity in treatment response is probably related to different molecular pathways or endotypes leading to eosinophilic airway inflammation, including adaptive immune pathways mediated by Th2 cells and innate immune pathways mediated by ILCs. Further studies are needed to define biomarkers or clinical characteristics that enable the most optimal allocation of patients to management with novel biologic agents.

The aim of the current review is to present one of the anti-IL-5R α mAb, benralizumab (Fasenra™). The mode of action, pharmacokinetics, pharmacodynamics data, efficacy and safety in clinical trials and thus applicability of benralizumab in the management of severe asthma are discussed. Benralizumab received US FDA approval on 14 November 2017, for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. In January 2018 it was announced that the European Commission approved benralizumab in the EU as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists.

Mechanism of action

Benralizumab (MEDI-563, BIW-8405) is a humanized mAb of IgG₁ κ type which is able to bind to the IL-5R α chain, thus blocking the typical IL-5/IL5R activation pathway. The α chain of IL-5R exclusively binds to IL-5 and its expression is found mainly on eosinophils and basophils in humans. As a result of the inhibition of IL-5 pathway, an impact on proliferation and maturation of eosinophil precursors in bone marrow, and on the migration, activation and apoptosis of mature cells at the site of inflammation is found [4–7]. Benralizumab is also characterized by high affinity for the Fc γ receptor found on cells involved in apoptosis such as NK lymphocytes, macrophages and neutrophils. This remarkable feature of benralizumab is enhanced by afucosylation. The structure of the antibody is characterized by lack of fucose sugar residue in the CH₂ region. Such an afucosylated IgG₁ κ mAb binds with the RIIIa region of Fc γ , thus strongly inducing ADCC of eosinophils. This explains properties of benralizumab to target circulating, as well as tissue-resident eosinophils. This mAb induces depletion of eosinophils in circulation, bone marrow and target tissues, which is in contrast with the mechanisms of action of other anti-IL-5 biologics (mepolizumab and reslizumab) which block the activation of eosinophils by neutralizing circulating IL-5 without any impact on resident eosinophils apoptosis. *In vitro* in primary human eosinophils and basophils benralizumab induced ADCC [8]. Preclinical studies on a monkey model showed that this mAb at different doses (0.1, 1, 10 and 30 mg/kg intravenously [iv.] administered every 3 weeks for 3 months) binds to and epitope on IL-5R α close to the IL-5 binding site, and is able to markedly reduce blood eosinophils and eosinophil precursors in the bone marrow [8]. Pham *et al.* [9] evaluated possible impact on biomarkers associated with eosinophilic inflammation in patients with asthma receiving benralizumab. Baseline and post-treatment levels of blood eosinophils, IL-5, eosinophil-derived neurotoxin (EDN), eosinophil cationic protein, eotaxin/chemokine (C-C motif) 11 (CCL11), eotaxin-2/CCL24, TNF and IFN- γ were analyzed. Increased EDN concentrations were found in sera of asthmatic subjects compared with healthy volunteers ($p < 0.05$). Correlation of serum EDN with blood eosinophil counts ($r_s = 0.5$; $p < 0.05$) was observed at baseline. Benralizumab induced reduction in blood eosinophil numbers, sera EDN and eosinophil cationic protein as compared with baseline ($p < 0.05$). No changes in TNF or IFN- γ were found, while serum IL-5, eotaxin/CCL11 and eotaxin-2/CCL24 increased after benralizumab administration versus placebo ($p < 0.05$). Authors discussed that observed increase in IL-5 concentrations with eosinophil reduction should not be regarded as unexpected as similar phenomenon was reported in murine models of eosinophil-ablated mice and in patients with eosinophilic syndromes treated with mepolizumab and could be explained by a reduction of target receptor-expressing immune cell subtypes. In summary, in contrast to mAbs that bind the IL-5 ligand, benralizumab binds to the IL-5R not the IL-5 only, blocking the action of cytokine and the effector cells. Moreover, benralizumab is inducing eosinophil apoptosis via ADCC. Thus, benralizumab does not result in the upregulation of IL-5, IL-5R expression or eosinophil activation, as occur with the anti-IL-5 mAbs. As a consequence the possible rebound effect in eosinophilic inflammation after cessation of the therapy may be significantly lower [4]. It could be concluded that benralizumab has potentially advantageous biological effects compared with other drugs targeting IL-5; however, it should be clearly stated that these effects have not, as yet, translated to any obvious clinical advantage.

Pharmacokinetics & pharmacodynamics data

The pharmacokinetics and pharmacodynamics data of benralizumab have been extensively presented elsewhere [10,11]. In short, after intravenous administration of benralizumab within dosing range of 0.03–3 mg/kg the elimination half-life is close to 18 days and volume of distribution equals 52–93 l/kg which is consistent with the IgG antibody [11]. In the Wang *et al.* study for the subcutaneous (sc.) dosing of benralizumab, the estimated

systemic clearance is 0.323 l/day [10]. The mean absorption time of subcutaneously administered benralizumab is 3.97 days. The dose proportional pharmacokinetics of benralizumab is likely associated with rapid depletion of target receptor pool on eosinophils in the blood. Stochastic stimulations supported selection of three dosages (2, 20 and 100 mg sc.) and every 8 week dosing for further clinical studies. In a small subgroup of patients receiving benralizumab treatment antidrug antibodies (ADAs) were detected. In those with high ADAs titers (≥ 400), the clearance of benralizumab was elevated 4.6-fold. The incidence and possible impact of ADAs on benralizumab mode of action needs to be evaluated in further clinical trials.

Clinical studies

Key clinical studies on efficacy of benralizumab in the management of asthma have been presented below and in **Table 1**. Busse *et al.* [11] in 2010 reported on a pilot trial of safety, pharmacokinetics and biologic activity of benralizumab (coded as MEDI-563). Single, escalating, intravenous doses of benralizumab (0.0003–3 mg/kg) were administered to patients diagnosed with mild, atopic asthma. It has been found that the peripheral blood eosinophil levels decreased in a dose-dependent manner, and eosinopenia lasted at least 8–12 weeks with dosages greater than 0.03 mg/kg. The safety profile was acceptable. Another of the first Phase I studies to evaluate the safety, tolerability and effects of benralizumab has been registered at the clinicaltrials.gov in 2008 with the identifier number NCT00659659 [12,13]. The primary outcomes included the safety and tolerability of MEDI-563 in adults with atopic asthma, and the effects of MEDI-563 on eosinophil counts in airway mucosal biopsies 28 days after completion of dosing. Secondary outcomes were defined as evaluation of pharmacokinetics and the immunogenicity of the studied compound. Twenty-seven adults (aged 18–65 years) with confirmed diagnosis of stable asthma, with at least 2.5% of eosinophils in sputum, were included and allocated to two cohorts. The first one received a single dose of benralizumab 1 mg/kg iv., and the other one received multiple dosages of benralizumab 100 or 200 mg given via subcutaneous injections in each cohort blinded with placebo. A decrease (18.7% at day 21 for cohort 1, and 89.9% at day 28 for cohort 2) in sputum and 100% decrease in blood eosinophils count was found. The active treatment resulted in significant reduction of eosinophilic airway inflammation as compared with placebo (in cohort 1 from 43.3/mm² to 15.6/mm² at day 28 and in cohort 2 from 63.6/mm² to 2.7/mm² at day 84). Pooled data from both cohorts at day 28 of dosing showed a significant difference between benralizumab and placebo (4.7% increase in placebo group vs 83.1% decrease in eosinophils in benralizumab cohort; $p = 0.02$). Authors concluded that a single intravenous dose and multiple subcutaneous dosing of benralizumab leads to reduced eosinophil counts in airway mucosa/submucosa and sputum, and a suppression of bone marrow eosinophil counts. Castro *et al.* [14] reported on a Phase IIb dose-ranging study in which patients were defined as ‘eosinophilic’ or ‘noneosinophilic’ with the use of the eosinophil/lymphocyte and eosinophil/neutrophil index and exhaled NO levels (cut-off point $< \text{or} \geq 50$ ppb). ‘Eosinophilic’ subjects were allocated to three different benralizumab treatment arms: 2, 20 or 100 mg, ‘noneosinophilic’ patients received 100 mg of benralizumab, all given subcutaneous first three doses every 4 weeks and then every 8 weeks for 1 year, blinded with placebo. Benralizumab was found to reduce exacerbation rates in eosinophilic cohort by 41% (80% CI: 11–60; $p = 0.096$) in the 100 mg group, but not in the 2 mg group (–9%, 80% CI: –59–26; $p = 0.781$) or the 20 mg group (reduction 36%, 80% CI: 3–58; $p = 0.173$), as compared with placebo. In patients with a baseline blood eosinophil cutoff of at least 300 cells/ μ l, exacerbation rates in the benralizumab 20 mg group was reduced by 57% ($p = 0.015$), and in the 100 mg group by 43% ($p = 0.049$), thus authors concluded that benralizumab 20 and 100 mg resided at the dose-response plateau. In the ‘noneosinophilic’ patients who received 100 mg of the active agent asthma exacerbations’ rate was reduced by 22% and did not reach the statistical significance ($p = 0.284$).

Two main clinical studies of benralizumab in asthma are known under acronyms of CALIMA and SIROCCO. In the report by Fitzgerald *et al.* [15] (CALIMA), patients aged 12–75 years with severe asthma, uncontrolled by medium-to-high dose of inhaled corticosteroids (ICS) plus long-acting β_2 -agonists, and a history of at least two exacerbations in the previous year were included and randomly assigned (1:1:1) to receive as add on treatment benralizumab 30 mg sc. every 4 weeks (Q4W), benralizumab 30 mg sc. every 8 weeks (Q8W; first three doses 4 weeks apart), or placebo for 56 weeks. Adolescents recruited in the EU countries were assigned only to benralizumab Q8W regimen (first 3 doses given Q4W) or placebo in line with the suggestion by the Pediatric Committee at the EMA to limit drug burden in adolescents. Patients were stratified (2:1) by baseline blood eosinophil counts 300 cells/ μ l or greater and less than 300 cells/ μ l. In total, 2505 patients were screened in 303 clinical centers in 11 countries, of whom 1305 were randomized to the study arms. The primary outcome was the annual rate of exacerbations defined as use of systemic corticosteroids, emergency department/urgent care visit or hospitalization. Secondary end points

Table 1. Summary of key clinical studies on efficacy and safety of benralizumab in asthma.

Study	Study population	Study design	Dosing	Key results	Ref.
Castro <i>et al.</i>	Adult (18–75 years) patients with uncontrolled asthma despite medium to high-dose ICS plus LABA, eosinophilic status defined by the use of the ELEN index, and FeNO	Randomized, controlled, double-blind, dose-ranging Phase IIb study	2, 20, 100 mg of benralizumab or placebo sc., every 4 weeks (Q4W) for the first three doses, followed by every 8 weeks for 1 year	609 patients; 41% decrease in exacerbations in the 100 mg dosing cohort, but no significant changes in the 2 and 20 mg groups; in patients with blood eos ≥ 300 cells/ μ l 57 and 43% reduction in exacerbations in 20 and 100 mg cohorts Nasopharyngitis (11 vs 6%, benralizumab vs placebo) and injection site reactions (16 vs 4%) more common in the active treatment	[14]
FitzGerald <i>et al.</i> CALIMA trial	12- to 75-year-old patients with severe asthma uncontrolled by medium-to-high dose of ICS plus LABA, history of ≥ 2 exacerbations in the previous year	Randomized, double blind, parallel-group placebo controlled, Phase III study, 303 sites, 11 countries	30 mg sc. Q4W or every 8 weeks (Q8W, first three doses Q4W) versus placebo, for 56 weeks	1306 patients; Q4W 36% and in Q8W 28% decrease in exacerbation rate, significant improvement in prebronchodilator FEV1 and total asthma symptom score (Q8W only) Nasopharyngitis and worsening of asthma as most common AE, same distribution in placebo and active treatment arms	[15]
Bleecker <i>et al.</i> SIROCCO trial	As above	As above, 374 sites in 17 countries	As above, for 48 weeks	1205 patients; 45% (Q4W) and 51% (Q8W) reduction in exacerbations rate, significant improvement in prebronchodilator FEV1 and asthma symptoms (only Q8W group) Worsening of asthma and nasopharyngitis reported as most common AE, same distribution in placebo and active treatment arms	[16]
Ferguson <i>et al.</i> BISE trial	Adult (18–75 years) patients with mild-to-moderate asthma defined by treatment (low-to-medium dose ICS) and symptomatic despite the treatment	Randomized, double-blind, placebo-controlled, Phase III trial	30 mg sc. Q4W for 12 weeks	211 patients; 80 ml improvement in prebronchodilator FEV1, no difference in total asthma symptom score, asthma control and quality of life between the active treatment and placebo Nasopharyngitis and respiratory tract infections reported as the most common AE, same distribution in the placebo and active treatment arms, 2 severe AE, considered unrelated to treatment	[20]
Nair <i>et al.</i> ZONDA trial	Adult patients with severe steroid-dependent asthma treated with medium-to-high dose ICS plus LABA. Patients received oral glucocorticoids for at least 6 months before enrollment	Randomized, double-blind, placebo-controlled Phase III trial	30 mg sc. Q4W or Q8W (first 3 doses Q4W) for 28 weeks	220 patients, 75% reduction in median oral glucocorticoid dose, significant decrease in exacerbation rates by 55% (Q4W) and 70% (Q8W), no impact on FEV1 Frequency of AE similar in placebo and active treatment groups	[21]

AE: Adverse event; ELEN: Eosinophil/lymphocyte and eosinophil/neutrophil index; Eos: Eosinophil; FeNO: Fraction of exhaled nitric oxide; FEV1: Forced expiratory volume in 1 s; ICS: Inhaled corticosteroid; LABA: Long-acting β_2 -agonist.

were prebronchodilator forced expiratory volume in 1 s (FEV1) and total asthma symptom score, for patients with blood eosinophil counts of at least 300 cells/ μ l (the intention to treat population). Patients included into the study were characterized by prebronchodilator FEV1 close to 60%, eosinophil count approximately 370 cells/ μ l (~ 500 eos/ μ l in the eosinophil ‘enriched’ population and ~ 160 – 190 eos/ μ l in the eosinophil ‘low’ cohort), BMI ca 29 kg/m² and almost three exacerbations in the preceding year. Benralizumab was found to significantly decrease exacerbation rates with the Q4W regimen (rate 0.60 [95% CI: 0.48–0.74]) and Q8W regimen (rate 0.66 [95% CI:

0.54–0.82]), as compared with placebo (rate 0.93 [95% CI: 0.77–1.12]); however, significant beneficial effects on exacerbations were only seen in the subgroup on high dose inhaled steroids at baseline. The active treatment resulted in significant improvement of prebronchodilator FEV1 (Q4W and Q8W study arms) and total asthma symptom score (Q8W arm only). In the SIROCCO study [16], the same as in the CALIMA project inclusion criteria resulted in enrollment of 1205 patients with similar clinical characteristics as in the described above trial. The dosing schemes were similar with the key difference in the duration of the study limited here to 48 weeks (56 weeks in the CALIMA trial). Benralizumab, as compared with placebo, significantly reduced the annual asthma exacerbation rate over 48 weeks when given Q4W (rate ratio: 0.55; 95% CI: 0.42–0.71; $p < 0.0001$) or Q8W (rate ratio: 0.49; 95% CI: 0.37–0.64; $p < 0.0001$). Both benralizumab dosing regimens significantly improved prebronchodilator FEV1 (least-squares mean change from baseline: Q4W group 0.106 l, and Q8W group 0.159 l). Asthma symptoms were improved by the Q8W regimen, but not the Q4W regimen.

The *post hoc* subanalysis of the both Phase III SIROCCO and CALIMA studies was performed [17] with the main goal to understand the efficacy and safety of benralizumab in patients with eosinophil-driven disease with blood eosinophil counts lower than 300 cells/ μ l. The effect of applying an eosinophil cutoff counts ≥ 150 versus < 150 cells/ μ l was thus evaluated. It has been found that benralizumab reduced asthma exacerbation rates by 42% in SIROCCO (rate ratio: 0.58; 95% CI: 0.46–0.74; $p < 0.001$; $n = 325$) and 36% in CALIMA (rate ratio: 0.64; 95% CI: 0.50–0.81; $p < 0.001$; $n = 300$) versus placebo ($n = 306$ for SIROCCO and $n = 315$ for CALIMA) for patients with blood eosinophil counts ≥ 150 cells/ μ l. Benralizumab increased prebronchodilator FEV1 (both studies, $p \leq 0.002$) and improved total asthma symptom score in SIROCCO ($p = 0.009$) at end of treatment versus placebo. Authors concluded that benralizumab is clearly effective in patients with asthma and blood eosinophil counts ≥ 150 cells/ μ l. In the yet another, recently published, pooled analysis of the results from the SIROCCO and CALIMA trials [18] the outcome defined as annual exacerbation rate ratio versus placebo was analyzed in subgroups defined by baseline eosinophil counts (≥ 0 , ≥ 150 , ≥ 300 or ≥ 450 cells/ μ l) and by number of exacerbations (two vs three or more) during the year before the enrollment. Exacerbation rate in patients with baseline eosinophil count ≥ 0 eosinophils/ μ l was 0.75 (95% CI: 0.66–0.84) in patients who received benralizumab every 8 weeks and 0.73 (95% CI: 0.65–0.82) in those who received the active treatment every 4 weeks, thus significantly lower as in the placebo group (1.16 [95% CI: 1.05–1.28]). What is interesting, the reduction rate was clearly greater with increasing blood eosinophil thresholds and with higher number of exacerbations. It has been concluded that results of this analysis may be helpful in our everyday clinical practice to guide allocation of patients with severe, uncontrolled asthma to the treatment with benralizumab.

In a small study (110 patients included), Nowak *et al.* [19] evaluated the ability of a single dose of benralizumab (0.3 mg/kg or 1.0 mg/kg iv.) to impact the recurrence during 12 weeks of follow-up after an acute asthma exacerbation. This study did not meet its primary end point of percentage of patients with ≥ 1 exacerbations at 12 weeks for the combined benralizumab groups compared with placebo. Compared with placebo benralizumab treatment resulted in reduction of exacerbation rate by 49% ($p = 0.01$), and exacerbations resulting in hospitalizations by 60% ($p = 0.02$).

Ferguson *et al.* [20] assessed safety and efficacy of benralizumab in patients with mild to moderate, persistent asthma (BISE trial). The severity of asthma was defined by medications used. Patients included were receiving low-to-medium dosage of ICS or low dosage ICS in combination with long-acting β_2 -agonists, had morning FEV1 50–90% of predicted and were symptomatic (reported daytime or night asthma symptoms, used rescue medications or had awakenings due to asthma) during the last week before randomization. Based on this inclusion criteria, 106 patients received benralizumab (30 mg sc. every 4 weeks for 12 weeks) and 105 were allocated to placebo arm. The primary end point was defined as an improvement in lung function. It has been found that benralizumab resulted in an 80 ml greater improvement in prebronchodilator FEV1 after 12 weeks of treatment as compared with placebo. There were no difference in total asthma symptom score, asthma control and quality of life between the active treatment and placebo. Benralizumab reduced median blood eosinophil counts to 0 cells/ μ l as compared with 230 cell/ μ l in the placebo group. The depletion of blood eosinophils was maintained to week 20 of the follow-up (8 weeks after termination of the active treatment). Authors concluded that this study proved that benralizumab is able to modify the disease process also in mild-to-moderate asthma. However, taking into consideration that improvements reported were not within the range of clinically important difference, probably in this population further studies are needed.

In the study by Nair *et al.* (ZONDA trial) [21], the possible impact of benralizumab on reduction of oral corticosteroid dose in patients suffering from severe asthma was evaluated. A total of 220 subjects were randomized

to benralizumab (30 mg sc. every 4 or every 8 weeks [first three doses given every 4 weeks]) or placebo. At week 28, a significant reduction in the median dose of oral glucocorticoid was found in benralizumab-treated patients (75% vs baseline in the active treatment, vs 25% in the placebo group; $p < 0.001$). The rate of asthma exacerbations was 55% lower (vs placebo) in the benralizumab 4 weeks dosing scheme, and 70% lower (vs placebo) in the benralizumab 8 weeks dosing scheme. In regards of the secondary end points, the lung function was not significantly improved in the active treatment as compared with placebo. Of note is that asthma control and health-related quality of life were better in the benralizumab 8 weeks dosing scheme ($p < 0.05$ vs placebo), but not for the benralizumab at 4 weeks dosing intervals. The presented study confirmed reports from previous clinical trials in regards of impact of benralizumab on exacerbations in severe asthma. Oral glucocorticoid therapy in this cohort of patients is associated with significant burden of adverse effects, thus oral glucocorticoids sparing effect of benralizumab cannot be underestimated.

The effect of benralizumab in an East-Asian population of subjects suffering from uncontrolled eosinophilic asthma has been evaluated [22]. The asthma exacerbation rate was reduced by 33, 45 and 36% versus placebo in the 2, 20 and 100 mg benralizumab cohorts, respectively. Findings of this study and the range of impact of benralizumab on exacerbations' number is in line with CALIMA and SIROCCO trials, which confirms applicability of this therapy in the Asian population.

The role of eosinophilic inflammation and especially association of airway eosinophilia with frequency of exacerbations have been recently extensively discussed not only in pathomechanisms of asthma but also in COPD. In this light, the study by Brightling *et al.* [23] with the primary goal to evaluate impact of benralizumab on the exacerbations rate in COPD is of special interest. Adult patients with COPD, with at least one exacerbation in the previous year and a sputum eosinophil count of at least 3% were included and randomized to benralizumab 100 mg sc. (every 4 or every 8 weeks, $n = 51$ subjects) or placebo ($n = 50$ subjects). Benralizumab did not reduce the rate of exacerbations in the per-protocol population (rates 0.95 vs 0.92, benralizumab vs placebo, respectively). However, in a subgroup analysis in patients with baseline blood eosinophils $\geq 200/\mu\text{l}$ and $\geq 300/\mu\text{l}$ there was a clear trend (not statistically significant probably due to low number of subjects in these subgroups) to decrease in number of exacerbations (by 31 and 58% vs placebo, in $\geq 200/\mu\text{l}$ and ≥ 300 eosinophils/ μl cohorts, respectively). Similarly, numerical but nonsignificant improvements were found in subjects with higher blood eosinophils in the Saint George's Respiratory Questionnaire, Chronic Respiratory Questionnaire and FEV1. The results of this study suggest that in a subgroup of COPD patients with increased levels of eosinophils, anti-IL5 therapy may be clinically effective, which is in line with previous reports on the potential role of another anti-IL-5 mAb – mepolizumab in COPD [24]. Phase III studies for COPD are currently ongoing.

Safety

First data on safety of benralizumab was reported in the Phase I trials. In the study by Laviolette *et al.* [12,13], described in detail above, the incidence of all adverse events (AEs) was similar between the placebo and benralizumab groups after both intravenous and subcutaneous administration. The most common AEs reported in the benralizumab group were nasopharyngitis (25%), headache (25%) and nausea (22.2%). In general, the incidence of AEs was found to be higher in the benralizumab than in the placebo group in the intravenous dosing (17 vs 27 events, placebo vs benralizumab, respectively) but not in the multiple subcutaneous dosing (20 vs 15 vs 10 events in placebo vs benralizumab 100 mg and benralizumab 200 mg dosing groups). What is interesting, 100% of subjects from the placebo group reported at least one AEs, but only approximately 60% of those receiving benralizumab. It could be concluded that none of AEs reported in this early phase study seemed to be clearly associated with the study compound. No apparent trends or markedly abnormal findings in serum chemistry, hematology or other lab tests was found. Of course, further studies in patients with longer exposure to benralizumab are needed to draw final conclusions regarding safety of the compound. In the Phase IIb dose-ranging study [14], in general, all AEs and all serious AEs were equally distributed in the placebo and benralizumab treatment arms. In details, nasopharyngitis was reported by 11% of patients receiving benralizumab versus 6% in the placebo group, and injection site reactions occurred more frequently with benralizumab than with placebo (16 vs 4%, benralizumab vs placebo, respectively).

In the Phase III CALIMA study [15], the number of AEs and serious AEs did not differ between placebo and benralizumab treatment arms. Nasopharyngitis (90 [21%] in the Q4W group, 79 [18%] in the Q8W group and 92 [21%] in the placebo group), followed by decrease in asthma control (61 [14%] in the Q4W group, 47 [11%] in the Q8W group and 68 [15%] in the placebo group) were among the most commonly reported AEs. Injection-site reactions and any hypersensitivity reactions (including potentially drug-related hypersensitivity) were

Table 2. Benralizumab compared with other anti-IL-5 monoclonal antibodies.

Monoclonal antibody	Mechanisms of action	Dosing	Key clinical features
Benralizumab	Humanized, monoclonal IgG ₁ κ type antibody, binding the IL-5R α chain, strongly inducing ADCC of eosinophils and basophils	30 mg sc. every 8 weeks (first three doses given every 4 weeks)	Decreases blood eosinophils and basophils close to the detection limits, reduces eosinophil precursors in the bone marrow by 80%, significantly reduces rate of exacerbations in severe asthmatics, shows clear oral-glucocorticoid sparing effect, good safety profile. US FDA and EU approval
Mepolizumab	N-glycosylated IgG ₁ κ humanized, monoclonal antibody with high affinity and specificity for circulating IL-5	100 mg sc. every 4 weeks	First anti-IL-5 mAb, several clinical studies proved its efficacy and safety in management of severe eosinophilic asthma, significant impact on exacerbation rate and clear oral-glucocorticoid sparing effect, good safety profile. FDA and EMA approval
Reslizumab	IgG ₄ κ humanized, monoclonal antibody with high affinity and specificity for circulating IL-5	3 mg/kg BW iv. every 4 weeks	Several efficacy and safety profile data available. FDA approval. The intravenous administration may be a limiting factor in clinical practice as compared with other anti-IL-5 mAbs

BW: Body weight; IL-5R: IL-5 receptor; mAb: Monoclonal antibody.

equally distributed in the placebo and active treatment arms. Similarly in the SIROCCO trial [16], the number of any AEs or any serious AEs did not differ between placebo and treatment arms. The most common events reported were asthma, nasopharyngitis and upper respiratory site infections. No increase in risk of site injection reactions or hypersensitivity reactions in the active treatment as compared with placebo was found. In the mild-to-moderate asthma cohort (BISE trial) [20] nasopharyngitis (8%) and upper respiratory tract infections (5%) were found with the same frequency in both benralizumab and placebo cohorts. Safety aspects of long-term benralizumab treatment are under evaluation in the BORA extension study (NCT02258542) in which patients from the SIROCCO, CALIMA and ZONDA trials will be followed up for up to two additional years. The estimated study completion date is set on 9 July 2018.

In patients with COPD [23], incidence of AEs was similar in benralizumab and placebo cohorts, with the most commonly reported respiratory disorders (63 vs 62%, benralizumab vs placebo, respectively) and infections (53 vs 56%, benralizumab vs placebo, respectively). Serious AEs were more common in the active treatment arm (14 vs 9 in the placebo group), although none of these events was considered by investigators to be related to benralizumab.

It should be kept in mind that significant abolition of eosinophils due to anti-IL-5 treatment may have some impact on host defense, for example, against parasitic infections. Further studies and clinical observation in this area are needed.

Conclusion

The results of the studies presented above confirmed effectiveness of benralizumab in the management of severe asthma. Benralizumab significantly reduces the rate of asthma exacerbations (Figure 1A) and has a clear oral glucocorticoid sparing effect. Published trials do not raise any safety issues as the frequency and the type of reported AEs do not differ between active treatment and placebo arms. Pilot studies show potential impact of benralizumab on pathomechanisms involved in mild-to-moderate asthma and COPD. The key features of benralizumab compared with other anti-IL5 mAbs are summarized in Table 2. In a systematic review and meta-analysis of efficacy and safety of anti-IL-5 therapy (mepolizumab, reslizumab and benralizumab) [25], 20 studies involving 7100 patients were included. In general, a clear and significant impact of anti-IL-5 therapy on exacerbations (44% reduction, risk ratio: 0.66 [0.59–0.73]), lung function (FEV₁, FEV₁% predicted) and asthma-related quality of life was found. There was no effect on rescue medication use and bronchial hyperreactivity. Anti-IL-5 therapy was not associated with increase of AEs (relative risk [RR] = 0.93; 95% CI: 0.89–0.98). When comparing the impact of individual antibodies on exacerbations in asthma, risk ratios versus placebo were 0.70 for benralizumab as compared with 0.62 for mepolizumab and 0.63 for reslizumab (Figure 1B). Similarly, yet another meta-analysis of ten trials involving 3421 patients [26] found on average 40% decrease in exacerbations by anti-IL-5 treatment. The patterns and rates of AEs reported were similar between the three drugs and placebo. The subgroup analysis revealed a slight additional improvement in the treatment effects in eosinophilic (defined as > 300 cells/ μ l) severe asthma patients. In conclusion, there are no doubts that benralizumab represents an effective and safe treatment of severe asthma.

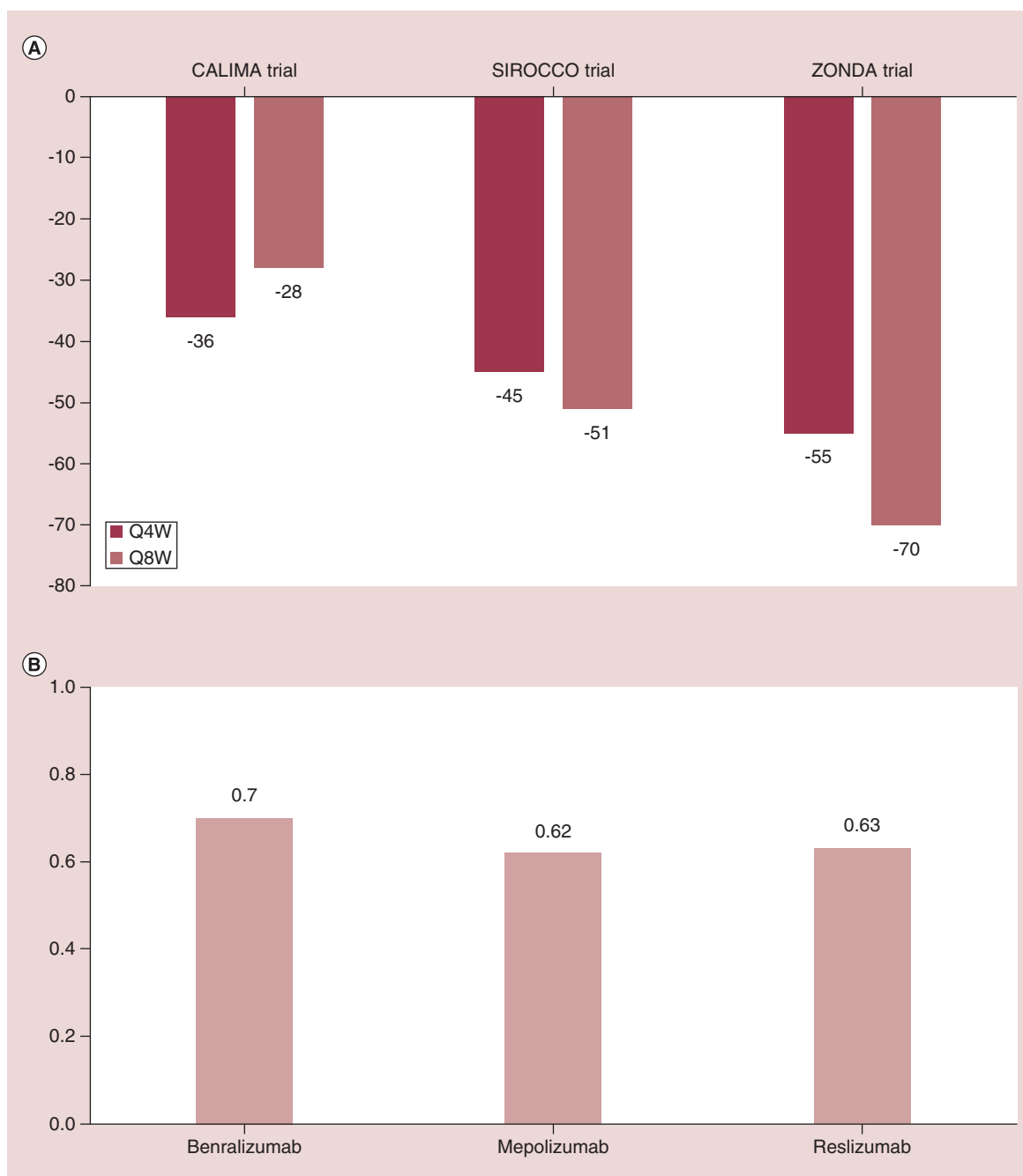


Figure 1. Efficacy of benralizumab in the management of asthma. (A) Impact of benralizumab on the exacerbations rate in asthma expressed as percentage of reduction rate versus placebo (Q4W – benralizumab 30 mg sc. every 4 weeks, Q8W – benralizumab 30 mg sc. every 8 weeks [16,25,21]). **(B)** The effect of anti-IL-5 therapies on exacerbation in asthma (expressed as relative risk vs placebo). Based on meta-analysis of published clinical studies [25].

Future perspective

Benralizumab proved its high efficacy and safety in the management of severe asthma. In the nearby future, pharmacoeconomy studies will show how decrease in exacerbation rate, systemic corticosteroid use and improvement in asthma control translates into savings in healthcare resource utilization. With increasing number of biologic agents available on the market probably costs of mAbs therapy will significantly decrease. It is nowadays well accepted that due to heterogeneity of asthma ‘one size fits all’ management of the disease is no longer valid. Future studies will improve identification of those subgroups, phenotypes or endotypes of asthma subjects with optimal

response to benralizumab therapy. Preliminary data suggest that the role of eosinophils as key biomarkers associated with disease course, prognosis and especially allocation to treatment in lung diseases will be increasing. Possibly other, easily accessible, noninvasive biomarkers associated with eosinophilic inflammation will be identified and introduced into clinical practice. As there is a clear overlap between the therapeutic potential of anti-IL-5 mAbs and other biologics, including anti-IgE – omalizumab, anti-IL-13 – tralokinumab, lebrikizumab, anti-TSLP mAbs clinical or real-life trials are needed to improve allocation of particular patient to the most optimal management. Future studies will improve our knowledge on the role of eosinophils in other lung disease (including COPD) bypassing access to anti-IL-5 therapy in other disorders including hypereosinophilic syndromes and eosinophilic granulomatosis with polyangiitis.

Executive summary

Eosinophils in inflammation

- IL-5 is vital for production, maturation, recruitment and survival of eosinophils at the site of inflammation. Eosinophils play a key role in inflammation underlying pathomechanisms of asthma, allergic disorders and other lung diseases, especially in severe asthma with frequent exacerbations.

Anti-IL-5 therapy

- Novel biologic agents including anti-IL-5 antibodies (mepolizumab and reslizumab) as well as anti-IL-5 receptor α chain (benralizumab) have been developed.

Mechanism of action of benralizumab

- Benralizumab is a humanized, monoclonal IgG₁ κ type antibody, binding the IL-5 receptor α chain, strongly inducing ADCC of eosinophils and basophils.

Preclinical studies

- Benralizumab leads to reduced eosinophil counts in airway mucosa/submucosa and sputum, and a clear inhibition on eosinophil differentiation and maturation in the bone marrow.

Clinical studies

- Benralizumab significantly reduces the rate of asthma exacerbations (SIROCCO and CALIMA trials) and has a clear oral glucocorticoid sparing effect in severe asthma (ZONDA trial). Post hoc analyses suggest that the effect of benralizumab on exacerbations' reduction rate is greater with increasing blood eosinophil thresholds and with higher number of previous exacerbations.

Safety of benralizumab

- Published trials do not raise any safety issues as the frequency and the type of reported adverse events do not differ between active treatment and placebo arms. Safety aspects of long-term benralizumab treatment are under evaluation in the BORA extension study in which patients from the SIROCCO and CALIMA trials will be followed up for up to two additional years.

Meta-analysis of clinical trials on anti-IL-5 therapy

- In meta-analysis of published clinical trials, when comparing the impact of individual antibodies on exacerbations in asthma, risk ratios versus placebo were 0.70 for benralizumab compared with 0.62 for mepolizumab, and 0.63 for reslizumab.

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Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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